EXHIBIT A

Effect of a fat spread enriched with medium-chain triacylglycerols and a special fatty acid-micronutrient combination on cardio-metabolic risk factors in overweight patients with diabetes [1,2,3]

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[8] **Abbreviations used:**

AGE, advanced glycation end products; ALAT, alanine-aminotransferase; ANCOVA, analysis of covariance; ApoB, apolipoprotein B; ASAT, aspartate-aminotransferase; BMI, body mass index; CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid, GFR, glomerular filtration rate; GGT, gamma glutamyl transferase; MDRD, Modification of Diet in Renal Disease; MCT, medium-chain triacylglycerols; MUFA, monounsaturated fatty acids; n-3-PUFA, omega-3 polyunsaturated fatty acids; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHtR, waist-to-height ratio

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Statement of author's contribution to manuscript

C. M. designed research. R. S. was involved in project conception and overall research plan.

C. E. analyzed dietary intake and conducted monitoring.

N. B. performed statistical analysis.

R. S., C. E. and C. M. wrote paper.

R. S. and C. M. have primary responsibility for final content. All authors read and approved the final manuscript.

56 **Abstract**

57

58 Medium-chain triacylglycerols (MCT) and omega-3 polyunsaturated fatty acids (n-3-
59 PUFA) are suggested to be useful for weight management and cardio-metabolic risk
60 reduction. As abdominal obesity is prevalent in patients with type 2 diabetes, the aim of
61 this controlled, double-blind study was to investigate the effect of a fat spread enriched
62 with MCT and a special fatty acid-micronutrient combination on cardio-metabolic risk
63 factors in overweight diabetic patients. 54 patients were randomized to receive either a
64 fat spread with 6 g/d MCT (MCT30%) or 1.2 g/d (MCT6%); 43 completed the study.
65 Analysis was performed according to the median of MCT intake (supplemented and
66 food-derived MCT). Clinical, anthropometric, blood, 24h-urine parameters and dietary
67 intake were assessed at baseline and after 12 weeks, respectively. Total MCT intake
68 >7g/d (MCT>7 group) significantly reduced waist circumference (WC) by 1.81 ± 2.69 cm,
69 whereas ≤7 g/d MCT (MCT≤7 group) increased WC by 0.32 ± 3.03 cm (p=0.027), which
70 is supported by a change in waist-to-height ratio (WHtR) (p=0.018). Fasting serum
71 triglycerides (TG) increased in both groups over time due to dietary habits. On the
72 contrary, diabetic metabolic situation and urinary albumin excretion did not change
73 during the intervention. Urinary pH differed significantly between both groups after 12
74 weeks. Intake of > 7 g/d MCT reduced WC in overweight diabetic patients. Other cardio-
75 metabolic risk factors were not affected by intervention due to negative changes in
76 macronutrient intake. Therefore, the suitability of a fat for nutrient enrichment remains to
77 be challenged. Further studies in alternative low-fat matrices are desirable.

Introduction

Evidence indicates the importance of abdominal adipose tissue as endocrine tissue to be a key for cardio-metabolic risk factors (1). Among patients with type 2 diabetes the combination of abdominal enlargement and hypertriglyceridemia, so called "hypertriglyceridemic waist" (HW)[8], is highly prevalent (2) and has been associated with a greater degree of subclinical atherosclerosis that may be related to the proatherogenic lipoprotein changes (3, 4). This lipoprotein changes called atherogenic dyslipidemia are typically characterized by reduced levels of high-density lipoprotein cholesterol (HDL C), elevated TG, and an increase in small, dense low-density lipoprotein (LDL) particles (5). HW has also been proposed to be an important factor increasing C-reactive protein (CRP) levels and relative coronary risk in patients with type 2 diabetes of any age and sex (6, 7). Moreover, reactive oxygen species are produced in various tissues under diabetic conditions leading to an antioxidant depletion and increased lipid oxidation, advanced glycation end products (AGE), cell damage and endothelial dysfunction (8, 9).

A supplementation of MCT for conventional dietary fats has been proposed as beneficial for weight management, since MCT are rapidly absorbed and preferentially transported through the portal venous system to the liver. The subsequent stimulation of hepatocytic β-oxidation may reduce the circulating fatty acids available to the adipocytes (10). Moreover, MCT enhances energy expenditure following thermogenesis (11, 12, 13).

The cardio-metabolic protective effects of omega-3 polyunsaturated fatty acids (n-3-PUFA) appear to be due to a synergism between multiple mechanisms that involve

antiinflammatory, inflammation-resolving, regulation of transcription factors and gene expression, membrane fluidity and antiarrhythmic and antithrombotic effects (14). Moreover, n-3-PUFA, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been demonstrated to exert beneficial effects in lowering TG levels (15), including in patients with atherogenic dyslipidemia associated diabetes (16, 17).

As fat spread is an important source of fat in the diet, the choice of a spread providing a high-quality fat and micronutrient profile may be an important dietary measure for patients with diabetes. Fat spreads characterized by a combination of MCT, n-3-PUFA and micronutrients have not been evaluated so far in this cohort. Therefore, aim of this study was to assess the benefit of a fat spread characterized by the above mentioned combination on cardio-metabolic risk factors in overweight diabetic patients.

Methods

Participants

Overweight diabetic patients were recruited from the region of Altomuenster, Bavaria, Germany. Both men and women aged 30 to 82 years with a body mass index (BMI) of 27 kg/m² or greater and a WC ≥ 94 cm for women and ≥ 102 cm for men were included into the study. Overweight diabetic patients were defined by clinical criteria. Individuals taking any medication or nutritional supplements for weight reduction were excluded. Further exclusion criteria comprised the supplementation and/or therapy with marine n-3-PUFA, micronutrients, treatment with glitazones and/or telmisartan, insulin-dependent

126 diabetes, ketoacidosis and acute or chronic diarrhoea. Characteristics of patients are
127 shown in Table 2. The study was approved by the Ethics Committee of the Bavarian
128 Chamber of Physicians, Munich, Germany, and all patients provided informed consent
129 before study onset.
130
131 *Study design*
132 This prospective study was carried out in a double-blind controlled manner. Patients
133 were randomly assigned to receive fat spread with either 6 g/d (MCT30%) or 1.2 g/d
134 MCT (MCT6%), which were equally enriched with special unsaturated fatty acids and
135 micronutrients (Table 1). Patients were asked to consume 2 x 15 g/d of the fat spreads
136 (MCT30% or MCT6%, respectively) for 12 weeks as substitution for their usual dietary
137 spread and to maintain their common diet and physical activity level during the study.
138
139 Data were analyzed at baseline and 12 weeks of intervention. Body weight (kg), height
140 (cm) and WC (cm) were measured to the nearest 0.1. Measurement of WC was
141 documented by photography. Anthropometric measurements and venous blood samples
142 were performed in the morning after an overnight fasting period of at least 12 h. Dietary
143 intake data (3-day food record) was analyzed using PRODI 5.5 software (WVG,
144 Stuttgart, Germany). The average of three days was assessed. Glomerular filtration rate
145 (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study
146 equation (18). Compliance was monitored by weighing of returned spread tubs at week
147 8 and 12 of intervention as well as by evaluating dietary records on which the number of
148 spread servings per day were recorded. Analysis was performed according to the
149 median of MCT intake (supplemented and food-derived MCT), which was 7 g/d MCT.

Laboratory methods

SYSCOMP GmbH, Augsburg, Germany, conducted all laboratory analyses. Analysis of serum and 24h-urine parameters were performed by standard methods with the exception of: HbA1c, turbidimetric immunologic inhibition assay (TINIA); Insulin, ECLIA; Cholesterol, CHOD-PAP method; LDL C and HDL C; enzymatic colour test; triglycerides, GPO PAP method CRP sensitive, turbidimetry from 22th of September 2009 on.

Statistical methods

All data are presented as means ± standard deviation. Significance was set at p-value 0.05 (two-sided). Changes of WC and body weight from baseline were determined using non-parametric analyses (exact Mann-Whitney-U-test). Pre-post intervention changes of all other variables were analyzed via non-parametric Wilcoxon test and inter group differences were compared using Mann-Whitney-U test. ANCOVA including use of WC change as a covariate was used to control for the potential confounder of serum fasting TG. Data analysis was performed based on the per protocol population and by using SPSS® for Windows (version PASW 18.0).

Results

Participants

A total of 54 overweight diabetic patients were recruited, of whom 43 were included into the per protocol (PP) population (24 men and 19 women). Reasons for an exclusion from the PP population included poor compliance as determined by more than 20% variance of product consumption (n = 7) and variation in study duration of more than 7 days (n = 2). Moreover, 2 patients left the study due to personal reasons. Both fat spreads were well tolerated by the patients and the majority of patients followed the treatment without any reported difficulty.

At baseline, both groups did not differ regarding anthropometric, clinical and biochemical parameters (Table 2). Metformin was used as anti-diabetic medication by 20 and sulfonylurea by 13 patients. Statins were taken as cholesterol-lowering medication by 11 and antihypertensive medication (beta-blocker, angiotensin converting enzyme inhibitors and calcium channel blocker) by 49 patients.

Clinical measurements

A total MCT intake > 7 g/d (n = 21) significantly reduced WC by 1.81 ± 2.69 cm (p = 0.005), whereas no significant change was observed in the MCT≤7 group (n = 22) (0.32 ± 3.03 cm, p = 1.000) over time (Table 2). The inter-group changes differed significantly (p = 0.027). Additionally, a significant difference in waist-to-height ratio (WHtR) was observed between groups (p = 0.018), whereas BMI and body weight changes did not

change significantly. Systolic and diastolic blood pressure remained unaffected by the supplementation in both groups.

Serum parameters

The average value of fasting TG was below the cut-off level of 150 mg/dL in the MCT>7 group (147.3 ± 92.0 mg/dL), whereas the fasting triglyceride level of the MCT≤7 group was hypertriglyceridemic (166.5 ± 113.3 mg/dL) (Table 2). Over time, fasting TG increased significantly in both groups ($p = 0.021$ and $p = 0.022$, respectively), but there was no inter-group difference. Total cholesterol, LDL-C, HDL-C, and TC/HDL-C ratio did not change during supplementation. Fasting glucose, insulin, HOMA index, glycated hemoglobin (HbA1c) and CRP were elevated in both groups during the study, but were not affected by intervention. The same applies to aspartate-aminotransferase (ASAT) and alanine-aminotransferase (ALAT), however gamma-glutamyltransferase (GGT) increased significantly in the MCT≤7 group ($p = 0.023$). In the MCT≤7 group, uric acid increased significantly during supplementation ($p = 0.024$), but remained within the normal range.

Urine parameters

Whereas no changes were observed for GFR, urinary albumin and sodium excretion, urinary pH varied significantly between groups after 12 weeks of intervention ($p = 0.032$) (Table 2).

Dietary intake

Except for the MCT intake, there was no significant difference in nutrient consumption between the both groups (Table 3). However, the relation of macronutrients shifted due to changes in dietary habits. Fat intake and percentage of energy consumed from fat increased during supplementation, however this change was not significant in the MCT>7 group. Saturated fat intake was found to be significantly elevated in the MCT>7 group by 7.3 ± 11.7 g/d ($p = 0.016$), mainly due to supplementation. PUFA consumption increased significantly only in the MCT>7 group ($p = 0.033$), whereas MUFA intake, including oleic acid, was significantly higher following the fat spread consumption in both groups ($p < 0.039$ and 0.010, respectively). The same applied for daily oleic acid, ALA, EPA and DHA intake. Glucose, fructose, sorbitol and purine intake remained stable over time. However, the fat spread consumption affected daily vitamin supply, as revealed by a significant increase in vitamin D, B2 and folic acid intake after 12 weeks in both groups. Vitamin E intake rose in the MCT>7 group, and nicotinic acid as well as vitamin B6 consumption were significantly enhanced over time in the MCT≤7 group.

Discussion

To our knowledge this is the first study investigating the effect of a fat spread enriched with MCT and a special fatty acid-micronutrient combination on cardio-metabolic risk factors in overweight diabetic patients. The major finding of the present study was a significant decrease in WC in the MCT>7 group. The reduction in WC observed in this study is in accordance with previous research evaluating the effect of MCT in overweight

239 subjects (19, 20, 21). The supplementation of 5 g/d MCT in form of an oil for instance
240 resulted in a significant WC decrease compared to the LCT control treatment (-5.1 ± 3.1
241 cm vs. -3.3 ± 1.9 cm, $p < 0.05$) (19). Tsuji et al. (21) reported a significant reduction in
242 WC by 5.67 ± 0.05 cm with BMI ≥ 23 kg/m^2, however only in the area of subcutaneous
243 fat, at a total daily MCT intake of 9.24 g/d.
244
245 Since some evidence also pointed at a beneficial effect on satiety (22), it has been
246 proposed that under free living conditions an increase in dietary MCT may result in less
247 energy intake and contributes to weight management. However, the fact that we did not
248 observed any decrease in energy intake and no change in body weight suggests that
249 the observed effect on WC may be rather ascribed to an effect on energy expenditure
250 and thermogenesis than to an increase in satiety (13, 23, 24).
251
252 Since long-chain PUFA are proposed to reduce TG, we hypothesized that the
253 intervention may involve an improvement in dyslipidemia. However, in our study the
254 consumption of the fat spreads did not result in any reductions in blood lipids. In
255 contrast, we observed a significant rise in fasting TG in both groups after
256 supplementation. It is suggested that fasting TG may have been affected by changes in
257 dietary habits regarding the quantity and quality of fat intake. Fatty acid intake profile of
258 patients revealed a rise in the intake from MUFA, especially oleic acid, in both groups.
259 Table 4 shows that TG-lowering effect could be attributed only to MCT intake, whereas
260 MUFA increased serum TG.
261

262 This rise in fat consumption may have counteracted any beneficial effects of the n-3
263 PUFA and may have caused the adverse effect on fasting TG instead. It further
264 indicates that the spreadable fat has not fully been consumed as a replacement of other
265 fat in the diet as intended, but rather in addition. In deed, several patients reported that
266 the consumption of 30g/d of spread during the study was much higher than the amount
267 of spread they usually consume which was reflected in their dietary protocols. However,
268 observations in free-living conditions illustrated that users of plant sterol enriched
269 margarines generally consumed less than the 20g/d recommended by the
270 manufacturers. The average daily intake of phytosterol-enriched margarine ranged
271 between 9 and 14 g (25), indicating that the serving size chosen in this study may not be
272 consistent with habitual spread intake in Europe. Unpredictable effects such as changes
273 in physical activity and nutritional behaviour over time which are difficult to control for
274 may bias results even in carefully designed studies (26).
275
276 An additional effect on fasting TG may have been expected due to n-3 PUFA
277 supplementation with the fat spreads. With combined daily intake of 240 mg DHA + EPA
278 and 870/900 mg ALA, the n-3-PUFA intake may have been too low to produce a
279 significant triglyceride-lowering effect. The recommended daily intake of n-3-PUFA for
280 the treatment of hypertriglyceridemia is 2 to 4 g (15).
281
282 The consumption of the fat spreads did not have any adverse affects on fasting glucose,
283 insulin, HOMA index, HbA1c, ASAT or ALAT. As GGT increased in MCT≤7 group, no
284 general effect of MCT supplementation on GGT could be derived.
285

286 The observed reduction in urinary pH in the MCT>7 group may be referred to the fact
287 that MCT have a ketogenic character, as acetyl-CoA produced during medium-chain
288 fatty acid oxidation is directed towards ketone body production (10). Additionally, oral
289 administration of MCT leads to urinary elimination of C6, C8 and C10 dicarboxylic acid
290 (27, 28).
291
292 Since the fat spreads were also enriched with fat soluble vitamins A, D3 and E, their
293 consumption added to a significant increase in the daily supply of these essential
294 nutrients and thus, ameliorated antioxidant and vitamin D3 status. These changes may
295 exert favourable effects on cardio-metabolic risk factors (29, 30).
296
297 In summary, a daily intake of at least 7 g MCT beneficially affects visceral fat mass,
298 objectivised as WC, in overweight diabetic patients. As the daily intake of MCT through
299 the normal diet is relatively small, a moderate enrichment of food with MCT may
300 effectively contribute to achieve this required intake. The supply of MCT through
301 enriched fat spreads may be adequate for individuals who are used to consume a high
302 amount of spread on a daily basis. But, it may be reasonable to reassess the suitability
303 of a fat spread as matrix for MCT. As dietary counselling for diabetic patients includes
304 recommendations to reduce and modify the fat intake, alternative food matrices such as
305 oil and milk products may be interesting alternatives in order to ensure an healthy
306 overall diet.
307
308

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Table 1: Mean composition of the MCT30% and MCT6% fat spread per daily serving (2 x 15g)[1]

	MCT30%	MCT6%
Energy (kcal)	176	176
Carbohydrates (g)	0	0
Protein (g)	0	0
Fat (g)	19.5	19.5
Fatty acids		
SAFA (g)	8.7	7.2
- MCT (g)	6.0	1.2
- SAFA without MCT (g)	2.7	6.0
MUFA (g)	6.9	8.1
- Oleic acid (g)	6.6	7.8
PUFA (g)	3.9	4.2
- LA (g)	2.88	3.1
- ALA (g)	0.87	0.9
- EPA (g)	0.15	0.15
- DHA (g)	0.09	0.09
Trans fatty acids (g)	0.12	0.09
Cholesterol (g)	0.006	0.006
Micronutrients		
Vitamin A (µg RE)	240	240
Vitamin B1(mg)	0.45	0.45
Vitamin B2 (mg)	0.48	0.48
Nicotinic acid (mg)	4.95	4.95
Vitamin B6 (mg)	0.48	0.48
Folic acid (µg)	120	120
Vitamin B12 (µg)	1.95	1.95
Vitamin D3 (µg)	1.8	1.8
Vitamin E (mg)	3.3	3.3
Sodium (g)	0.002	0.002
Chrome (mg)	0.015	0.015
Manganese (mg)	0.6	0.6

[1] abbreviations used: ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linolenic acid; MCT, medium-chain triacylglycerols; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids ; RE, retinol equivalent; SAFA, saturated fatty acids

Table 2: Clinical and biochemical characteristics at baseline and after supplementation[1]

	MCT intake > 7 g/d (n = 21)				MCT intake ≤ 7 g/d (n = 22)				P[b]
	wk 0	wk 12	wk 12 – 0	P[a]	wk 0	wk12	wk 12 – 0	P[a]	
Weight (kg)	95.7 ± 21.2	95.3 ± 21.7	-0.35 ± 1.92	0.641	87.7 ± 11.6	88.3 ± 11.7	0.54 ± 1.76	0.118	0.177
BMI (kg/m²)	34.35 ± 6.84	34.23 ± 7.08	-0.12 ± 0.70	0.681	31.69 ± 4.05	31.89 ± 4.10	0.20 ± 0.61	0.092	0.174
WC (cm)	112.5 ± 12.5	110.7 ± 12.9	-1.81 ± 2.69	0.005	106.4 ± 6.6	106.7 ± 7.0	0.32 ± 3.03	1.000	0.027
WHtR	0.676 ± 0.076	0.665 ± 0.079	-0.010 ± 0.016	0.008	0.640 ± 0.045	0.642 ± 0.049	0.002 ± 0.018	0.920	0.018
SBP (mmHg)	138.6 ± 18.4	137.9 ± 12.0	-0.7 ± 13.2	0.792	148.4 ± 18.6	142.0 ± 17.2	-6.4 ± 15.4	0.069	0.249
DBP (mmHg)	84.8 ± 11.7	84.1 ± 7.7	-0.7 ± 10.3	0.707	87.7 ± 8.7	85.2 ± 8.7	-2.5 ± 9.2	0.170	0.612
Fasting TG (mg/dl)	147.3 ± 92.0	181.6 ± 122.7	34.2 ± 72.6	0.021	166.5 ± 113.3	216.6 ± 177.1	50.1 ± 108.1	0.022	0.990
TC (mg/dl)	209.5 ± 41.0	214.0 ± 41.6	4.52 ± 18.60	0.177	217.7 ± 37.9	225.4 ± 42.7	7.68 ± 23.04	0.058	0.527
LDL-C (mg/dl)	128.8 ± 34.9	130.7 ± 32.3	1.95 ± 16.59	0.357	136.4 ± 34.9	135.6 ± 40.1	-0.86 ± 22.04	0.848	0.618
HDL-C (mg/dl)	52.1 ± 10.8	49.7 ± 10.6	-2.39 ± 8.75	0.230	49.5 ± 9.9	51.4 ± 13.9	1.88 ± 6.71	0.363	0.085
TC/ HDL-C	4.15 ± 0.98	4.50 ± 1.37	0.35 ± 0.82	0.064	4.51 ± 1.01	4.65 ± 1.50	0.14 ± 0.70	0.637	0.289
Fasting glucose (mg/dl)	127.5 ± 21.8	132.0 ± 29.7	4.48 ± 19.91	0.422	124.4 ± 23.9	126.5 ± 34.6	2.09 ± 18.70	0.676	0.313
Fasting insulin (µU/ml)	12.6 ± 9.1	13.7 ± 11.0	1.09 ± 9.33	0.509	14.4 ± 6.8	17.6 ± 25.4	3.17 ± 24.16	0.299	0.177
HOMA-Index	4.14 ± 3.73	4.81 ± 5.52	0.68 ± 5.21	0.639	4.46 ± 2.39	5.72 ± 9.01	1.26 ± 8.68	0.306	0.234
HbA1c (%)	6.76 ± 0.58	6.69 ± 0.78	-0.067 ± 0.380	0.367	6.46 ± 0.47	6.46 ± 0.53	0.004 ± 0.208	0.844	0.179
CRP (mg/l)	6.17 ± 5.97	5.52 ± 4.91	-0.66 ± 2.77	0.140	5.80 ± 8.46	4.45 ± 4.63	-1.35 ± 6.76	0.274	0.961
Uric acid (mg/l)	5.96 ± 1.53	6.27 ± 1.52	0.31 ± 0.66	0.024	6.58 ± 1.26	6.58 ± 1.04	0.00 ± 1.09	0.944	0.103
GGT (U/l)	43.8 ± 50.1	41.2 ± 26.4	-2.57 ± 27.84	0.265	43.8 ± 47.6	44.2 ± 30.5	0.45 ± 20.82	0.023	0.442
ASAT (U/l)	28.4 ± 10.6	28.0 ± 8.3	-0.43 ± 5.97	0.861	28.1 ± 11.9	27.1 ± 6.5	-1.00 ± 9.01	0.480	0.643
ALAT (U/l)	33.5 ± 21.8	31.2 ± 14.3	-2.24 ± 9.96	0.650	29.2 ± 14.1	30.4 ± 13.8	1.18 ± 10.77	0.166	0.607
GFR (mL/min/1.73 m²)	87.9 ± 19.1	86.4 ± 22.4	-1.54 ± 11.28	0.433	81.7 ± 15.7	83.4 ± 14.9	1.71 ± 8.60	0.095	0.290
U-Albumin (mg/24h)	55.3 ± 199.4	19.5 ± 39.9	-35.8 ± 162.7	0.594	62.1 ± 225.8	60.0 ± 150.1	-2.1 ± 109.3	0.641	0.842
U-pH (24h)	5.81 ± 0.81	5.52 ± 0.73	-0.29 ± 0.70	0.062	5.80 ± 1.08	6.05 ± 1.12	0.25 ± 0.88	0.176	0.032
U-Sodium (mmol/24h)	212.0 ± 84.6	234.5 ± 89.0	22.5 ± 78.2	0.145	208.6 ± 67.6	231.0 ± 75.6	22.4 ± 72.2	0.153	1.000

[1] data are presented as mean ± SD
[a] p values for comparison between week 0 and 12 (Wilcoxon-Test),
[b] p value calculation for comparison between week 0 and 12 based on Mann-Whitney-U-Test

[2] abbreviations used: ASAT, aspartate-aminotransferase; ALAT, alanine-aminotransferase; CRP, C reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration rate; GGT, gamma-glutamyltransferase; HbcA1, glycated haemoglobin; MCT, medium chain triglycerols SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference; WHtR, waist to height ratio; U-albumin, urine albumin; U-pH, urine pH; U-sodium, urine sodium

Table 3: Daily dietary intake at baseline and after supplementation[1,2]

	MCT intake > 7g/d (n = 21)				MTC intake ≤ 7g/d (n = 22)				P[b]
	wk 0	wk 12	wk 12 – 0	P[a]	wk 0	wk 12	wk 12 – 0	P[a]	
Energy (kcal/d)	2341.9 ± 650.0	2440.4 ± 758.4	98.5 ± 601.3	0.566	2234.4 ± 950.3	2518.8 ± 1095.4	284.5 ± 1229.6	0.223	0.593
Protein (g/d)	95.6 ± 22.7	93.4 ± 40.7	-2.2 ± 37.9	0.498	90.6 ± 45.7	102.7 ± 57.6	12.1 ± 67.3	0.263	0.211
Protein (%EN)	16.89 ± 2.23	15.43 ± 2.90	-1.47 ± 2.92	0.027	16.27 ± 3.10	16.13 ± 2.72	-0.14 ± 3.55	0.592	0.198
Carbohydrates (g/d)	237.0 ± 59.3	237.2 ± 62.3	0.2 ± 58.1	0.931	240.9 ± 96.9	241.1 ± 86.0	0.2 ± 109.3	0.808	0.771
Carbohydrates (%EN)	41.42 ± 6.35	40.53 ± 7.14	-0.89 ± 5.83	0.715	44.79 ± 7.74	40.27 ± 7.65	-4.51 ± 7.53	0.014	0.076
Fat (g/d)	93.4 ± 30.4	106.6 ± 37.6	13.2 ± 30.2	0.068	89.1 ± 47.0	111.0 ± 57.6	21.9 ± 60.5	0.050	0.789
Fat (%EN)	36.4 ± 5.5	39.4 ± 4.7	3.03 ± 6.16	0.079	35.1 ± 6.2	39.1 ± 5.8	4.04 ± 6.04	0.006	0.423
Alcohol (g/d)	21.3 ± 35.4	19.3 ± 28.2	-1.96 ± 16.86	0.476	11.8 ± 20.2	17.9 ± 27.6	6.03 ± 24.84	0.227	0.206
Alcohol (%EN)	5.33 ± 7.61	4.66 ± 6.29	-0.67 ± 3.29	0.590	3.86 ± 6.05	4.48 ± 6.58	0.62 ± 5.65	0.872	0.771
Cholesterol (mg/d)	363.2 ± 145.2	393.6 ± 213.7	30.4 ± 160.4	0.543	332.4 ± 189.0	359.7 ± 193.7	27.2 ± 259.2	0.758	0.884
SAFA (g/d)	34.6 ± 13.9	41.9 ± 13.5	7.3 ± 11.7	0.016	32.4 ± 17.7	40.2 ± 18.8	7.8 ± 21.1	0.072	0.942
MCT (g/d)	1.31 ± 0.76	7.74 ± 0.56	6.43 ± 0.83	< 0.001	1.08 ± 0.64	4.94 ± 2.12	3.86 ± 2.29	< 0.001	< 0.001
MUFA (g/d)	34.0 ± 12.3	39.9 ± 16.0	5.9 ± 13.5	0.039	34.1 ± 19.9	45.5 ± 26.5	11.3 ± 27.1	0.010	0.627
PUFA (g/d)	14.5 ± 6.6	16.8 ± 5.7	2.3 ± 6.6	0.033	14.7 ± 7.7	18.2 ± 9.0	3.4 ± 9.5	0.082	0.981
Oleic acid (g/d)	30.1 ± 11.2	35.8 ± 14.4	5.7 ± 12.5	0.039	30.1 ± 17.7	40.7 ± 24.5	10.7 ± 24.6	0.011	0.610
LA (g/d)	12.34 ± 5.76	13.79 ± 4.98	1.45 ± 5.61	0.073	12.91 ± 6.88	15.21 ± 8.09	2.30 ± 8.30	0.322	0.981
ALA (g/d)	1.35 ± 0.82	2.09 ± 0.38	0.74 ± 0.78	0.001	1.15 ± 0.54	2.03 ± 0.66	0.88 ± 0.79	<0.001	0.409
LA/ALA	9.60 ± 1.87	6.47 ± 1.23	-3.14 ± 2.08	<0.001	11.37 ± 3.70	7.22 ± 1.70	-4.15 ± 3.43	<0.001	0.395
EPA (g/d)	0.040 ± 0.038	0.187 ± 0.035	0.147 ± 0.048	<0.001	0.035 ± 0.039	0.178 ± 0.027	0.143 ± 0.049	<0.001	0.981
DHA (g/d)	0.075 ± 0.085	0.192 ± 0.148	0.117 ± 0.167	0.003	0.068 ± 0.116	0.152 ± 0.071	0.083 ± 0.151	0.001	0.752
LA/(ALA+EPA+DHA)	8.72 ± 1.63	5.50 ± 1.11	-3.22 ± 1,65	<0.001	10.56 ± 3.67	6.20 ± 1.57	-4.35 ± 3.35	<0.001	0.296
Glucose (g/d)	11.4 ± 6.4	13.7 ± 6.1	2.3 ± 7.0	0.106	14.7 ± 7.4	13.7 ± 8.9	-1.0 ± 8.8	0.661	0.174
Fructose (g/d)	16.7 ± 10.4	17.7 ± 8.8	1.0 ± 11.6	0.532	20.2 ± 9.3	18.0 ± 11.1	-2.1 ± 12.2	0.527	0.296
Sorbitol (g/d)	1.01 ± 0.83	1.25 ± 1.12	0.24 ± 1.37	0.498	1.01 ± 0.58	1.70 ± 1.46	0.69 ± 1.49	0.051	0.437

Table 3: ... *continuation*

	MCT intake > 7g/d (n = 21)				MTC intake ≤ 7g/d (n = 22)				P^b
	wk 0	wk 12	wk 12 – 0	P^a	wk 0	wk 12	wk 12 – 0	P^a	
Retinol (RE µg/d)	3093.4 ± 6769.2	1671.6 ± 825.4	-1421.8 ± 6808.4	0.434	2611.9 ± 3613.9	1845.3 ± 792.9	-766.5 ± 3442.7	0.783	0.789
Vitamin D (µg/d)	3.09 ± 3.68	5.54 ± 4.76	2.45 ± 6.08	0.010	2.48 ± 3.58	3.54 ± 2.01	1.06 ± 4.36	0.042	0.627
Vitamin E (mg/d)	11.01 ± 5.25	14.45 ± 4.25	3.44 ± 4.66	0.004	12.10 ± 5.65	15.03 ± 7.19	2.92 ± 7.60	0.077	0.481
Vitamin B2 (mg/d)	1.77 ± 0.98	2.18 ± 0.65	0.41 ± 1.03	0.008	1.59 ± 0.72	2.26 ± 1.04	0.67 ± 1.24	0.006	0.752
Nicotinic acid (mg/d)	22.5 ± 8.8	25.9 ± 9.3	3.5 ± 12.2	0.217	19.5 ± 8.3	29.3 ± 15.0	9.8 ± 15.0	<0.001	0.159
Vitamin B6 (mg/d)	2.11 ± 0.80	2.52 ± 1.31	0.41 ± 1.17	0.122	1.98 ± 0.89	2.75 ± 1.31	0.77 ± 1.44	0.002	0.296
Folic acid (µg/d)	250.4 ± 157.3	354.1 ± 88.9	103.7 ± 119.1	0.001	239.5 ± 82.7	371.5 ± 139.4	131.9 ± 153.3	< 0.001	0.716
Vitamin B12 (µg/d)	11.14 ± 15.76	10.54 ± 4.74	-0.61 ± 16.15	0.063	8.65 ± 7.70	10.83 ± 5.19	2.18 ± 9.35	0.050	0.369
Vitamin C (mg/d)	92.8 ± 89.2	79.2 ± 29.6	-13.6 ± 86.0	0.848	88.9 ± 40.6	92.3 ± 48.5	3.4 ± 64.1	0.758	0.771
Sodium (g/d)	3.14 ± 1.23	3.02 ± 1.24	-0.12 ± 1.10	0.715	3.39 ± 1.87	3.50 ± 2.21	0.11 ± 2.54	0.485	0.716
Chloride (g/d)	4.74 ± 1.71	4.62 ± 1.84	-0.12 ± 1.51	0.741	5.03 ± 2.65	5.29 ± 3.38	0.26 ± 3.86	0.592	0.644
Salt (g/d)	7.1 ± 2.7	6.9 ± 2.8	-0.2 ± 2.4	0.715	7.5 ± 4.2	7.8 ± 5.1	0.4 ± 5.9	0.509	0.789
Fiber (g/d)	21.9 ± 11.7	22.2 ± 7.2	0.32 ± 8.96	0.434	24.1 ± 10.5	25.3 ± 13.4	1.16 ± 14.47	0.910	0.808
Purins (mg/d)	203.9 ± 67.0	201.9 ± 98.8	-2.0 ± 111.8	0.821	200.7 ± 98.6	230.1 ± 129.3	27.0 ± 145.5	0.327	0.464
Uric acid (mg/d)	613.4 ± 201.4	605.9 ± 297.7	-7.5 ± 336.1	0.794	586.3 ± 279.8	685.2 ± 352.7	98.9 ± 397.4	0.072	0.224

[1] data are presented as mean ± SD

[a] p values for comparison between week 0 and 12 (Wilcoxon-Test)

[b] p values for comparison of group x time interactions (Mann-Whitney-U-Test)

[2] abbreviations used: ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EN, energy; EPA, eicosapentaenoic acid; LA, linoleic acid; MCT, medium chain triacylglycerols; PUFA, polyunsaturated fatty acids; RE, retinol equivalent; SAFA, saturated fatty acids

Table 4: Serum fasting triglycerides depending on change of fatty acid intake[1]

ANCOVA	Oleic acid (g/d)	MUFA* (g/d)	PUFA (g/d)	MCT (g/d)	SAFA** (g/d)	Age (years)	Gender[2] (1 f/2 m)
PP (n = 43) p = 0.471	B: 0.789	B: 2.046	B: -1.710	B: -17.950	B: 0.324	B: -0.050	B: -72.396
	95% CI (-9.84;11.42)	95% CI (-44.8;48.9)	95% CI (-19.0;15.6)	95% CI (-42.1;6.2)	95% CI (-13.5;14.2)	95% CI (-6.2;6.1)	95% CI (-175.5;30.7)
	p = 0.881	p = 0.930	p = 0.842	p = 0.141	p = 0.962	p = 0.987	p = 0.163

*without oleic acid
**without MC
[1] abbreviations used: MCT, medium chain triacylglycerols; MUFA, monounsaturated fatta acids; PUFA, polyunsaturated fatty acids; SAFA, saturated fatty acids
[2] gender is coded by 1 (women) and 2 (men)

Online supporting material

Supplemental Figure 1: Trial profile